Remarks

Applicants thank the Examiner for withdrawal of the rejection under 35 U.S.C. § 103(a) over Tidmarsh in view of Kozyrev. Upon entry of the foregoing amendment, claims 1, 2, and 25 are pending in the application, with claim 1 being the independent claim.

Claim 1 has been amended. Support for the amendment of claim 1 is found throughout the specification and originally filed claims, specifically at Figure 4. This change is believed to introduce no new matter, and its entry is respectfully requested. Based on the following remarks, Applicants respectfully request that the Office reconsider the outstanding objection and rejection, and that they be withdrawn.

Priority Date for the Claims 1, 2 and 25

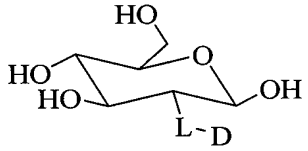
Applicants submit that claims 1, 2, and 25 are entitled to a priority date of at least February 27, 2004. The Office is of the opinion that:

> The provisional applications 60/476,648 [,filed June 9, 2003], 60/537,282 [,filed January 16, 2004], 60/540,700 [,filed January 30, 2004], and 60/548,240 [, filed February 27, 2004], upon which priority is claimed, fail to provide adequate support under 35 U.S.C. 112 for claims 1, 2, and 25 because of this application because none of the priority applications provides support for each of the structures presented in amended claim 1.
>
> Thus, the filing date of claims 1, 2, and 25 is deemed to be the instant filing date, June 9, 2004.

(Office Action, pages 2-3).

Applicants respectfully disagree with the Office's assertion that the priority date of claims 1, 2, and 25 is June 9, 2004, the filing date of the present application, for at least the reasons below.

Currently amended claim 1 is entitled to a filing date of at least February 27, 2004. Claim 1 recites:

> 1. A 2-deoxyglucose conjugate, wherein said conjugate is represented by the formula:
>
> 
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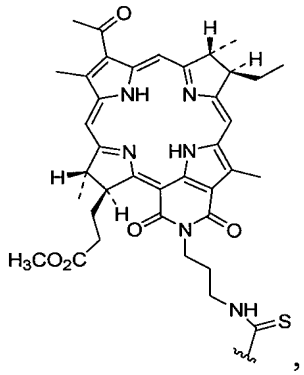
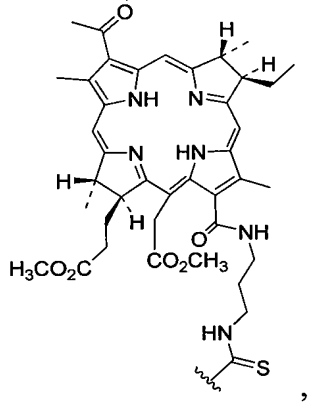
>
> or a pharmaceutically acceptable salt thereof, wherein L is a linker group; and D is selected from the group consisting of BChlPP of the formula
>
> 
>
>
> ,
>
> BChlE6 (bacteriochlorin e_6) of the formula
>
> 
>
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> and NIR664 (tricarbocyanine) of the formula
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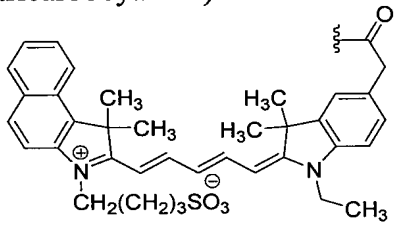
> 
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> .

Based on a review of provisional applications 60/476,648 ("the '648 application"), filed June 9, 2003; 60/548,240 ("the '240 application"), filed February 27, 2004; 60/540,700 ("the '700 application"), filed January 30, 2004; and 60/537,282 ("the '282 application"), filed January 16, 2004, Applicants submit that their disclosure provides a written description, and enables a person having ordinary skill in the art to make and use the currently claimed invention without undue experimentation.

The '240 application, filed February 27, 2004, describes 2-deoxyglucose conjugates attached to either BChlE6 (bacteriochlorin e_6) or BChlPP. (The '240 application, pages 1-9). Furthermore, the '282 application, filed January 16, 2004, describes a 2-deoxyglucose moiety attached to NIR 664, and the use thereof for imaging of tumors. (The '282 application, pages 1-8). Therefore, claim 1 satisfies the written description and enablement requirements of 35 U.S.C. § 112, para. 1. Accordingly, claim 1 is entitled to a filing date of at least February 27, 2004.

The additional limitations of claim 2 are disclosed in the '648 application. Claim 2 recites:

> 2. (original) The conjugate of claim 1, wherein said linker group, L, is selected from the group consisting of a covalent bond, -NH-, -peptide-, -nucleic acid-, -O-, $(CH_2)_r$—O-, -NH- CH_2- CH_2-NH-, -NH-CH(COOH)-CH_2-NH-, -NH-CH_2-CH(COOH)-NH-, -NH-CH_2-CH_2-CH_2-NH, -O-$(CH_2)_r$NH-, S-$(CH_2)_r$-NH-, -S-$(CH_2)_r$-C(O)-, -NH-CH_2-C(O)-, -O-CH_2-CH_2-O-CH_2-CH_2-O, -NH-NH-C(O)-CH_2-, -NH-C$(CH_2)_2$-C(O)-, and -NH-NH-C(O)-$(CH_2)_r$-C(O)NH-N=., wherein r, in each instance, is from 2-5.

Claim 2 depends directly from claim 1 and, therefore, contains each limitation of claim 1. *See* 35 U.S.C. § 112, ¶ 4. The '648 application discloses that the linker group (L) in the 2-deoxyglucose conjugate may be:

> L, is selected from the group consisting of a covalent bond, -NH, -peptide-, -nucleic acid-, -O-, $(CH_2)_r$—O-, -NH- CH_2- CH_2-NH-, -NH-CH(COOH)-CH_2-NH-, -NH-CH_2-CH(COOH)-NH-, -NH-CH_2-CH_2-CH_2-NH, -O-$(CH_2)_r$NH-, S-$(CH_2)_r$-NH-, -S-$(CH_2)_r$-C(O)-, -NH-CH_2-C(O)-, -O-CH_2-CH_2-O-CH_2-CH_2-O, -NH-NH-C(O)-CH_2-, -NH-$C(CH_2)_2$-C(O)-, and -NH-NH-C(O)-($CH_2)_r$-C(O)NH-N=, wherein r, in each instance, is from 2-5.

(The '648 application, pages 7-8, ¶ [0015]).

Therefore, claim 2 is entitled to a filing date of at least February 27, 2004.

Likewise, the additional limitations of claim 25 are disclosed in the '648 application. Claim 25 depends from claim 1, and recites: "A pharmaceutical composition comprising the conjugate of claim 1 and a pharmaceutically acceptable carrier." Pursuant to 35 U.S.C. § 112, ¶ 4, claim 25 includes each limitation of claim 1. The '648 application discloses that 2-deoxyglucose conjugates can be combined with one or more pharmaceutically acceptable diluents, carriers or excipients to form pharmaceutical compositions. (*Id.* at page 6, ¶ [0009]). Therefore, claim 25 is entitled to a filing date of at least February 27, 2004.

Rejections under 35 U.S.C. § 103(a)

The rejection of claims 1, 2 and 25, as allegedly being obvious over U.S. Patent No. 6,989,140 B2 ("Tidmarsh") in view of Fukuzumi, S. *et al., J. Phys. Chem. A., 106*:5105-5113 (2002) ("Fukuzumi") is respectfully traversed. (*Office Action, page 3*).

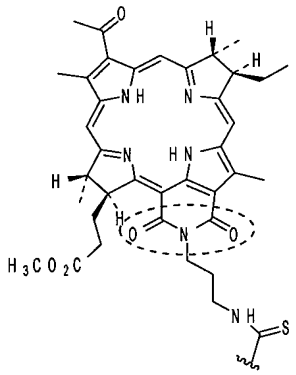
The basis of the Office's rejection of claims 1, 2, and 25 under 35 U.S.C. § 103(a) appears to be "(A) Combining prior art elements according to known methods to yield predictable results," known as Rationale A. *Manual of Patent Examining Procedure,* 8th edition, revision 6, 2100-128 *(August 2007)* ("MPEP"). To establish a *prima facie* case of obviousness under Rationale A, the Office must show that "the prior art included *each* element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference." *Id.* at 129 (emphasis added).

A *prima facie* case of obviousness for a chemical compound requires "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)). As such, "[o]bviousness based on structural similarity . . . can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound." *Eisai Co. Ltd. vs. Dr. Reddy's laboratories, Ltd.*, No. 2007-1397, slip op. at 4 (Fed. Cir. July 21, 2008) (Exhibit A) (citing *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007)).

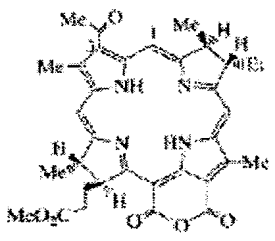
The Office has not established a *prima* facie case of obviousness, for at least the reasons below. The references cited by the Office—Tidmarsh and Fukuzumi—do not include all the elements of the claimed invention. First, by the Office's own admission, Tidmarsh does not teach all the elements of the

claimed invention. (*Office Action*, page 4). Furthermore, Fukuzumi does not cure the deficiencies of Tidmarsh and, in fact, does not teach a single element of the claimed invention. Indeed, the compounds described in Fukuzumi are structurally different from the claimed compounds. As illustrated below, the BChlPP group, as encompassed by the claimed invention, has an alkylaminothiocarbonyl group bonded to the nitrogen atom of the imide functional group (-(C=O)-N-(C=O)-). In contrast, in each of compounds 2-5 described in Fukuzumi, an unsubstituted alkyl (i.e. hexyl group) is attached to the nitrogen atom of the imide functional group (-(C=O)-N-(C=O)-). (Fukuzumi, page 5108).

BChlPP:



The following compounds were described in Fukuzumi:



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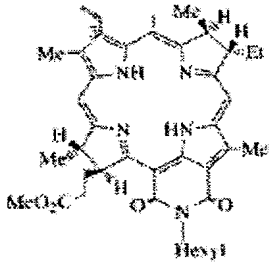

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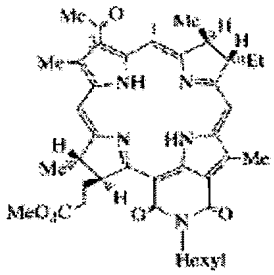

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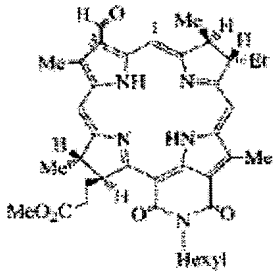

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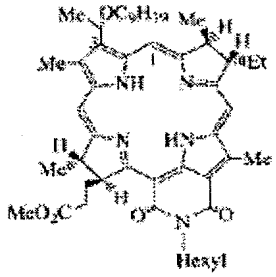

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Moreover, the Office has not provided a rationale or motivation that would have led one of ordinary skill in the art to select and then modify conjugates of Tidmarsh by attaching a compound described in Fukuzumi or an analog thereof.

Second, because of the unpredictability of the chemical arts, a person having ordinary skill in the art would not necessarily expect that chemical structures that are structurally similar would have the same properties. Here, the mere fact that compound 3 (as highlighted by the Office on page 5 of the Office Action) described in Fukuzumi is structurally similar to the BChlPP does not necessarily mean that a person having ordinary skill in the art would have had a rationale to modify compound 3 by replacing the simple alkyl group with the more complex alkylaminothiocarbonyl group. Moreover, a person having

ordinary skill in the art would not reasonably expect that such a modification would be successful in obtaining a compound with the same properties as that of compounds 2-5.

Third, the Office has not met its burden of providing a rationale as to why a person having ordinary skill in the art would modify the compounds of Tidmarsh and the compounds of Fukuzumi to arrive at the claimed invention. Specifically, the Office has not provided a rationale for modifying the compounds of Fukuzumi to arrive at the D groups encompassed by claim 1. Notably, the Office has not provided a rationale for modifying the Tidmarsh conjugates by replacing the fluorophore moiety with a Fukuzumi compound or for that matter, a Fukuzumi compound that was modified as described above. In addition, the Office has not shown that a person having ordinary skill in the art would reasonably expect that modifying the Tidmarsh conjugates by replacing the fluorophore moiety with a modified Fukuzumi compound would be successful in obtaining conjugates with the same properties as those of the claimed conjugates. According, it would not have been obvious to a person having ordinary skill in the art at the time the invention was made to prepare the claimed conjugates based on the teachings of Tidmarsh and Fukuzumi.

Based on the foregoing, Applicants respectfully request that the preceding rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Cynthia M. Bouchez
Attorney for Applicants
Registration No. 47,438

Date: February 4, 2009

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919920_1.DOC

EXHIBIT A

United States Court of Appeals for the Federal Circuit

2007-1397, -1398

EISAI CO. LTD. and EISAI, INC.,

Plaintiffs-Appellees,

v.

DR. REDDY'S LABORATORIES, LTD.
and DR. REDDY'S LABORATORIES, INC.,

Defendants-Appellants,

and

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellant.

Joseph M. O'Malley, Jr., Paul, Hastings, Janofsky & Walker, LLP, of New York, New York, argued for plaintiffs-appellees. With him on the brief were Bruce M. Wexler, David M. Conca, Gary G. Ji, and Quinn E. Clancy.

Maurice N. Ross, Budd Larner, P.C., of Short Hills, New Jersey, argued for defendants-appellants Dr. Reddy's Laboratories, Ltd., and Dr. Reddy's Laboratories, Inc. With him on the brief were Andrew J. Miller, Louis H. Weinstein, Ellen T. Lowenthal, and Dmitry V. Sheluho.

Henry C. Dinger, Goodwin Procter LLP, of Boston, Massachusetts, argued for defendant-appellant Teva Pharmaceuticals USA, Inc. With him on the brief were Elaine H. Blais, and David M. Hashmall, Frederick H. Rein, and Emily L. Rapalino, of New York, New York.

Appealed from: United States District Court for the Southern District of New York

Judge Gerard E. Lynch

United States Court of Appeals for the Federal Circuit

2007-1397, -1398

EISAI CO. LTD. and EISAI, INC.,

Plaintiffs-Appellees,

v.

DR. REDDY'S LABORATORIES, LTD.
and DR. REDDY'S LABORATORIES, INC.,

Defendants-Appellants,

and

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellant.

Appeals from the United States District Court for the Southern District of New York in case No. 03-CV-9053 and 03-CV-9223, Judge Gerard E. Lynch.

DECIDED: July 21, 2008

Before RADER, LINN, and PROST, Circuit Judges.

RADER, Circuit Judge.

On summary judgment, the United States District Court for the Southern District of New York found in favor of plaintiffs Eisai Co., Ltd. and Eisai, Inc. (collectively Eisai) with respect to the validity and enforceability of U.S. Patent No. 5,045,552 ('552 patent). Eisai Co. v. Teva Pharms. USA, Inc., No. 03 Civ. 9223 (S.D.N.Y. Oct. 5, 2006) (SJ Validity Order); Eisai Co. v. Dr. Reddy's Labs., Ltd., No. 03 Civ. 9053 (S.D.N.Y. Oct. 5,

2006) (SJ Enforceability Order). After a bench trial, the district court found that Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively Dr. Reddy's) and Teva Pharmaceuticals USA, Inc. (Teva) had failed to prove the remaining allegations of inequitable conduct, and that Eisai had established that Dr. Reddy's and Teva infringed Eisai's '552 patent. Eisai Co. v. Dr. Reddy's Labs, Ltd., No. 03 Civ. 9053 (S.D.N.Y. May 11, 2006) (Trial Order). Because the district court correctly determined that the '552 patent is non-obvious over the proffered prior art and that Eisai's alleged acts during prosecution did not rise to the level of inequitable conduct, this court affirms.

I

The '552 patent claims rabeprazole and its salts. Rabeprazole is part of a class of drugs known as proton pump inhibitors, which suppress gastric acid production by inhibiting action of the enzyme H^+K^+ATPase. The distinctions between rabeprazole and its salts are not relevant for this appeal. Therefore this court refers to rabeprazole and its salts collectively as "rabeprazole." Rabeprazole's sodium salt is the active ingredient in Aciphex, a pharmaceutical approved in 1991 by the FDA for the treatment of duodenal ulcers, heartburn, and associated disorders. Aciphex has been a commercial success, garnering over $1 billion in worldwide yearly sales.

Dr. Reddy's and Teva each filed Abbreviated New Drug Applications (ANDAs) under the Hatch-Waxman Act, 21 U.S.C. § 355 and 35 U.S.C. § 271(e), seeking to manufacture a generic version of Aciphex before the expiration of the '552 patent. Because filing an ANDA is an artificial, but legally cognizable, act of patent infringement, see Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1344 (2004), Eisai filed suit against Dr. Reddy's and Teva. Eisai also sued Mylan Laboratories Inc. and Mylan

Pharmaceuticals Inc. (collectively Mylan), another ANDA filer, but that proceeding was stayed pending the outcome of these actions. Mylan agreed to be bound by the final judgments and any appeals in these cases. Eisai Co., Ltd. v. Mylan Labs., Inc., No. 04 Civ. 656 (S.D.N.Y. Nov. 3, 2004). Both Dr. Reddy's and Teva conceded infringement of claims 1-6 of the '552 patent, but asserted that the '552 patent is unenforceable for inequitable conduct. Trial Order at 6-7. Dr. Reddy's stipulated to the validity of all six of the '552 patent's claims, id. at 6, but Teva argued before the district court and maintains on appeal that the '552 patent is invalid for obviousness. Both Dr. Reddy's and Teva appeal the trial court's judgments of enforceability. Neither Dr. Reddy's nor Teva appeals the trial court's judgment of infringement. This court has jurisdiction under 28 U.S.C. § 1295(a)(1).

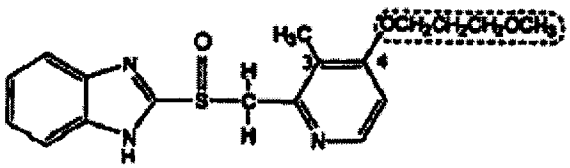
II

This court reviews a grant of summary judgment without deference. Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1362 (Fed. Cir. 2003). Obviousness under 35 U.S.C. § 103(a) is ultimately a legal question, based on underlying factual determinations. See Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997). The factual determinations underpinning the legal conclusion of obviousness include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). Thus, in reviewing a district court's summary judgment of non-obviousness, this court reviews the record for genuine issues of material fact without deference, bearing in mind the movant's

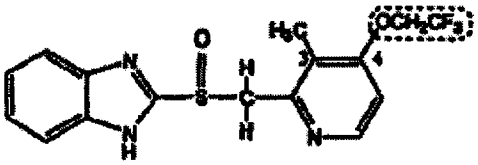
burden to prove invalidity by clear and convincing evidence. See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

Where, as here, the patent at issue claims a chemical compound, the analysis of the third Graham factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art compounds. See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1377 (Fed. Cir. 2006) (noting that, for a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions" (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))). Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007). In keeping with the flexible nature of the obviousness inquiry, KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007), the requisite motivation can come from any number of sources and need not necessarily be explicit in the art. See Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007). Rather "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." Id. (quoting Dillon, 919 F.2d at 692).

Teva asserts that a combination of three prior art references renders the '552 patent obvious: 1) European Patent No. 174,726 (owned by Takeda), claiming lansoprazole (EP '726); 2) United States Patent No. 4,255,431 (to Junggren), claiming omeprazole ('431 patent); and 3) an article by Brändström, et al., entitled "Structure Activity Relationships of Substituted Benzimidazoles" (Brändström). EP '726 teaches, inter alia, the ulcer treatment compound lansoprazole. Lansoprazole differs structurally from rabeprazole at the 4-position on the pyridine ring, as indicated in the diagram below. Lansoprazole has a trifluoroethoxy (OCH_2CF_3) substituent, whereas rabeprazole has a methoxypropoxy ($OCH_2CH_2CH_2OCH_3$) substituent.



Rabeprazole

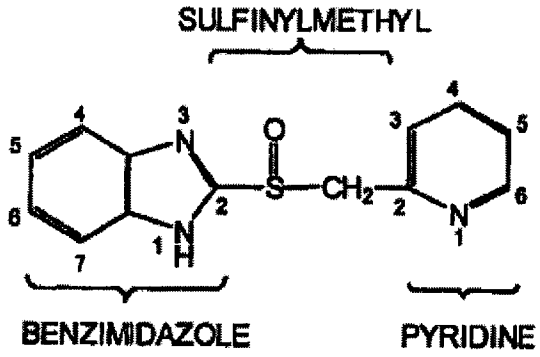


Lansoprazole

Appellant Teva's Br. at 28. Otherwise, the two compounds are identical. See SJ Validity Order at 7. Both rabeprazole and lansoprazole are "asymmetrically substituted" with respect to the 4-position on the pyridine ring because the substituent at the 3-position (a methyl group in both compounds) is not the same as the substituent at the 5-position (a hydrogen in both compounds).

The '431 patent discloses a broad class of gastric acid inhibiting compounds, including omeprazole, the first commercial proton pump inhibitor, sold as Prilosec. Although sharing the same basic structure, omeprazole is structurally farther afield from rabeprazole than is lansoprazole. For instance, omeprazole's pyridine ring is symmetrically substituted and has a methoxy (OCH_3) group at the 4-position.

Finally, Brändström describes a class of anti-ulcerative compounds having a benzimidazole-sulfinylmethyl-pyridine core (the Brändström core structure):



Brändström Core Structure

Rabeprazole, lansoprazole, and omeprazole are all Brändström core structure compounds. Taking the evidence in the light most favorable to Teva, this court assumes that as per EP '726, lansoprazole is twenty times superior to omeprazole for anti-ulcer action, as measured by an indomethacin-induced gastric lesion assay in rats. This court also assumes that lansoprazole has certain traits, including lipophilicity (the ability of a compound to cross lipid membranes) and low molecular weight, that would have made it desirable to a skilled artisan.

Under these assumptions, one of skill in this art may have considered it a candidate for a lead compound in the search for anti-ulcer compounds. To the contrary, the district court emphasized the differences between anti-ulcer action and gastric acid inhibition. The trial court specifically noted that Teva's expert testified with respect to the EP '726 data that "[t]he level of acid secretion . . . from these [anti-ulcer] data . . . cannot be determined." SJ Validity Order at 13. In this context, this court consults the counsel of KSR that "any need or problem known in the field of endeavor at the time of

invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." 127 S. Ct. at 1742. Thus lansoprazole's candidacy as a starting point to develop new anti-ulcer compounds versus new gastric acid inhibitors does not resolve the lead compound analysis, at least not in the absence of any contrary indications. Cf. Takeda, 492 F.3d at 1359 (negative side effects could dissuade one of skill from using a particular compound as a starting point).

Nonetheless, as the district court noted, the EP '726 reference teaches at best that the fluorinated substituent of lansoprazole provides "a special path to achieving lipophilicity." SJ Validity Order at 10 (emphasis in original). And Teva's expert identified a separate reference teaching that fluorine-substituted groups increase lipophilicity. Id. The record, however, shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property. Indeed, Teva's pharmacology expert, Dr. John Forte, declined to opine on lansoprazole's relevance to an examiner assessing the patentability of rabeprazole. J. A. at 14894. And Dr. Reddy's pharmacology expert, Dr. Simmy Bank, testified in deposition that "I thought [lansoprazole] had nothing to do with this trial." J. A. at 14756.

This court notes that the district court did not rigidly limit Teva's obviousness arguments by forcing Teva to select a single lead compound. Rather Teva alone selected lansoprazole as the anchor for its obviousness theory, not the district court. In KSR, the Supreme Court noted that an invention may have been obvious "[w]hen there [was] . . . a design need or market pressure to solve a problem and there [were] . . . a finite number of identified, predictable solutions." 127 S. Ct. at 1742 (tense changes

supplied to clarify, as the Court stated and as per 35 U.S.C. § 103, that the obviousness inquiry must rely on evidence available "at the time" of the invention, see Takeda, 492 F.3d at 1356 n.2). The Supreme Court's analysis in KSR thus relies on several assumptions about the prior art landscape. First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda, 492 F.3d at 1357 ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

In other words, post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound. Teva cannot create a genuine issue of material fact on obviousness through the

unsupported assertion that compounds other than lansoprazole might have served as lead compounds. Further, the record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution. In sum, the district court properly concluded that the record did not support a case of obviousness of the '552 patent as a matter of law.

III

As with other summary judgment issues, this court reviews a district court's summary judgment on inequitable conduct without deference. Innogenetics, N.V. v. Abbott Labs., 512 F.3d 1363, 1378 (Fed. Cir. 2008). In contrast, where a judgment regarding inequitable conduct follows a bench trial, this court reviews the district court's findings of materiality and intent for clear error and its ultimate conclusion for an abuse of discretion. ACCO Brands, Inc. v. ABA Locks Mfrs. Co., 501 F.3d 1307, 1315 (Fed. Cir. 2007).

Inequitable conduct in prosecuting a patent application before the United States Patent & Trademark Office may take the form of an affirmative misrepresentation of material fact, a failure to disclose material information, or the submission of false material information, but in every case this false or misleading material communication or failure to communicate must be coupled with an intent to deceive. Innogenetics, 512 F.3d at 1378 (citations omitted). Materiality, defined as "what a reasonable examiner would have considered important in deciding whether to allow a patent application," and intent are both questions of fact, and require proof by clear and convincing evidence. Id. To satisfy the "intent" prong for unenforceability, "the involved conduct, viewed in

light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." Kingsdown Med. Consultants, Ltd. v. Hollister Inc., 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc) (citing Norton v. Curtiss, 433 F.2d 779 (CCPA 1970)). Gross negligence is not sufficient. Id. This is a high bar.

On appeal, Teva and Dr. Reddy's allege that Eisai misled the Patent Office in five ways: 1) failing to disclose Eisai's own co-pending '013 application, which claimed the "ethyl homolog" of rabeprazole (compound SHKA 661); 2) withholding rejections from the '013 application's prosecution that also would have been applicable to the '552 patent's prosecution; 3) failing to disclose the prior art "Byk Gulden patent" (WO 8602646); 4) submitting a misleading declaration (the Fujisaki Declaration) to the examiner of the '552 patent; and 5) concealing lansoprazole from the examiner. The district court rejected the fifth assertion on summary judgment, SJ Enforceability Order at 58, and the other four after a bench trial, Trial Order.

Teva and Dr. Reddy's first and second allegations rely on Eisai's failure to disclose the fact of, and rejections contained in, Eisai's patent application claiming the "ethyl homolog" of rabeprazole. Known to Eisai's scientists as compound SHKA 661, the ethyl homolog differs from rabeprazole as its name suggests. SHKA 661 has one fewer methylene unit at the 4-position of the pyridine ring, giving SHKA 661 an ethoxy group rather than a propoxy group at this position. The district court correctly pointed out that calling SHKA 661 the "ethyl homolog" of rabeprazole in this case could carry a misleading implication with respect to inequitable conduct. The record supplies no evidence to suggest that Eisai's scientists ever referred to SHKA 661 by this name, or

thought of SHKA 661 and rabeprazole "primarily in relation to each other." Trial Order at 17 n.7. Rather, the district court found credible the testimony that Eisai scientists considered SHKA 661 separately patentable, even though Eisai ultimately did not pursue that course. Id. at 22-23; 42-43. Furthermore, even if a provisional obviousness-type double-patenting rejection might have issued in the prosecution of the '552 patent due to the co-pending SHKA 661 application, the district court found the materiality of this potential situation low, because applicants routinely overcome this type of rejection, id. at 44, by amending claims or filing a terminal disclaimer. Nonetheless, the district court did not hold that the fact of the copendency of these two applications to be totally immaterial, accurately noting that applicants should be encouraged to disclose closely related applications. Id. at 47.

While disclosure of the co-pending SHKA 661 application to the Patent Office during the prosecution of the '552 patent would have been prudent, Eisai's failure to do so is by no means fatal, for two reasons. First, the district court had ample evidence from which to conclude that the materiality of the SHKA 611 application was low, as outlined above. Second, the record is devoid of any real suggestion of intent to deceive the Patent Office, much less the clear and convincing evidence required to support a finding of inequitable conduct.

As for the rejections of the '013 application that would have been relevant to the prosecution of the '552 patent, the district court did not reach materiality because it discerned insufficient proof of intent to deceive. The district court found the documentary evidence (faxed exchange between Eisai employees Mr. Shuhei Miyazawa, one of the inventors of the '552 patent, and Mr. Mitsuo Taniguchi, Eisai's

patent agent, regarding Mr. Miyazawa's presentation to a pharmaceutical trade industry group) to supply no compelling evidence of intent, based on testimony from both parties to the fax. Witness credibility determinations lie squarely within the district court's discretion. See Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1171 (Fed. Cir. 2006). The district court was ultimately undisturbed by the Taniguchi/Miyazawa communication based on its evaluation of the witness testimony presented, and this court sees no abuse of discretion. These facts certainly do not rise to the level of "culpability" this court required in Kingsdown, 863 F.2d at 876, to establish intent to deceive, or even gross negligence.

Finally, the district court found that Teva's theory that Eisai deliberately hid the ball from the Patent Office by separately filing the '552 and '013 prosecutions to be "implausibly risky," given that such similar applications would usually be assigned to the same examiner in the same art unit. Trial Order at 53. The district court thus had ample bases from which to conclude that Eisai's failure to disclose its co-pending '013 application along with the rejections issued in its prosecution, while not completely forthcoming, did not rise to the level of inequitable conduct.

With respect to the Byk Gulden patent, Teva and Dr. Reddy's argue that Eisai's failure to disclose this reference to the Patent Office during prosecution of the '552 patent was material because a reasonable examiner would have used it to issue a new and stronger prima facie obviousness rejection on the basis of Byk Gulden's disclosure of asymmetrically-substituted compounds having a methoxyethoxy at the 4-position of the pyridine ring. But the district court found Byk Gulden's teachings cumulative with references already disclosed to the Patent Office (Junggren or Junggren combined with

Beecham). As per 37 C.F.R. § 1.56, cumulative evidence is definitionally not material evidence. See Monsanto Co. v. Bayer Bioscience N.V., 514 F.3d 1229, 1237 (Fed. Cir. 2008). Here, the Junggren reference specifically disclosed asymmetrically substituted compounds, including a compound having a 4-position methoxyethoxy substituent. Thus the Byk Gulden reference offered nothing new to the record already before the Patent Office. And even Teva's expert conceded Byk Gulden would not have provided the examiner with anything new. Id. at 57. Thus the district court was well within its discretion in concluding that the Byk Gulden patent was not material to the prosecution of the '552 patent. Even if Byk Gulden had been material, the lack of clear and convincing evidence of intent to deceive would nonetheless have imposed an insurmountable bar to finding inequitable conduct, for the reasons given by the district court.

As for the Fujisaki Declaration, Eisai submitted it during prosecution to overcome an obviousness rejection. Because this reference shows rabeprazole's pharmacological properties, the trial court found it highly material. Id. at 59. Teva and Dr. Reddy's argue that the data presented in the Fujisaki Declaration were misleading. They contend that the comparison with two non-prior art compounds without a comparison of the ethyl homolog of rabeprazole, SHKA 661, sent the examiner on a dead-end side trip. The district court properly characterized this argument as "contorted." Id. The Fujisaki Declaration indisputably showed a comparison between rabeprazole and the prior art compound called out by the examiner, demonstrating rabeprazole's superiority. Further, as discussed above, the materiality of SHKA 661 and the patent application claiming it was low. The data from the Fujisaki Declaration

were relevant to prosecution, but Eisai had no obligation to include additional, unnecessary data such as a comparison to SHKA 661. Thus the district court did not abuse its discretion in concluding that Eisai did not commit inequitable conduct in failing to include additional data in the Fujisaki Declaration to the examiner. Even here, where the submission to the Patent Office itself was highly material to prosecution, the lack of deceptive intent rendered stillborn yet another allegation of inequitable conduct.

Finally, Teva and Dr. Reddy's assert that that Eisai deceptively declined to inform the examiner of a patent application for lansoprazole, a prior art proton pump inhibitor (and the active ingredient in Prevacid). The district court disposed of this argument on summary judgment. The district court found that Teva and Dr. Reddy's had presented neither direct evidence of deceptive intent nor any evidence to support an inference of materiality. SJ Enforceability Order at 58. The strongest evidence of some problem was the passing comment of one Eisai "insider" that the similarity of lansoprazole and rabeprazole "bothers me." Id. at 59. But this vague, subjective statement is not sufficient by any means to establish materiality, let alone intent. Moreover, given lansoprazole's fluorinated substituent and its resultant impotence to render the '552 patent invalid, the district court properly rejected this strained theory of inequitable conduct on summary judgment.

IV

In a series of thoughtful, thorough opinions, the district court carefully explained its reasoning with respect to both obviousness and inequitable conduct. Because the district court properly concluded that Teva and Dr. Reddy's failed to prove that the '552

patent was invalid for obviousness or unenforceable for inequitable conduct, this court affirms the district court's judgment.

AFFIRMED

COSTS

Each party shall bear its own costs.